

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2005/050412

International filing date (day/month/year)
01.02.2005

Priority date (day/month/year)
04.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07D237/04, C07D401/12, C07D403/12, A61K31/50, A61K31/501, A61P11/08

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Scruton-Evans, I

Telephone No. +49 89 2399-8272



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/050412

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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10/587830

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15,16

because:

☒ the said international application, or the said claims Nos. 15,16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-16
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-16
Industrial applicability (IA)	Yes: Claims	1-14
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15,16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the Search report are referred to in this communication;

- D1: EP-A-0 738 715 (MERCK PATENT GMBH) 23 October 1996 (1996-10-23)
- D2: EP-A-0 618 201 (MERCK PATENT GMBH) 5 October 1994 (1994-10-05)
- D3: WO 02 085885 A (SCHMIDT BEATE ;ALTANA PHARMA AG (DE);
GRUNDLER GERHARD (DE); STERK) 31 October 2002 (2002-10-31)
- D4: MEY VAN DER M ET AL: 'Novel Selective PDE4 nhibitors. 1 Synthesis,
Structure-Activity Relationships, and Molecular Modeling of 4-(3,4-
Dimethoxyphenyl)-2H-p hthalazin-1-ones and Analogues' JOURNAL OF
MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON,
US, vol. 44, no. 16, 2001, pages 2511-2522, XP002222830 ISSN: 0022-2623
- D5: WO 03 032993 A (MERCK PATENT GMBH ;WOLF MICHAEL (DE);
EGGENWEILER HANS-MICHAEL (DE) 24 April 2003 (2003-04-24)

With regard to the requirement for novelty (Article 33(2) of the PCT), the compounds of the present application differ from those of the prior arts essentially in the groups R1 and R2 in the present application. Article 33(2) of the PCT is thus satisfied.

With regard to the requirement for inventive step (Article 33(3) of the PCT), the compounds of the present application are described as being PDE4 inhibitors. The prior arts D1-D5 all disclose the same qualitative activity for structurally similar compounds. It can be seen from these prior arts that various modifications can be made to the core structure, without loss of the qualitative activity. Document D1 teaches that the 4 position may be unsubstituted, mono or di substituted, as does D2 (albeit with a different 2-position moiety), and D3 teaches the use of the groups R3 and some of R9 of the present application. D4 teaches that the 4 and 5 positions may be unsubstituted or mono-substituted. Thus the man skilled in the art, faced with the problem of providing further novel PDE4 inhibitors, would have had sufficient incentive from the prior arts to prepare the compounds of the present application, especially given the teachings of D1 and D4, and the fact that a fused ring structure is also compatible with activity (see D3), expecting them to have a qualitative activity. The problem underlying the invention must therefore have been the provision of further compounds with unexpected advantages re the closest prior art (considered to be D1). Indeed it is stated in the description that the compounds of the present application have surprising and particularly advantageous properties. This is, however, not substantiated, and no comparison has been carried out to show in what way the properties are surprising. Thus at the present time, inventive step cannot be acknowledged, as the evidence required to show that the problem as defined above has been solved is not available. Suitable favourable comparisons with the prior art could be sufficient for acknowledgement of inventive step (Article 33(3) PCT).

For the assessment of the present claims 15,16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

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Re Item VIII

Certain observations on the international application

Certain of the definitions of R9 are not covered by the priority document.